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(71) Applicant *(for all designated States except US)*: MEIJI MILK PRODUCTS CO., LTD. [JP/JP]; 3–6, Kyobashi 2–chome, Chuo–ku, Tokyo 104–0031 (JP).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: LUU, Bang [FR/FR]; Centre de Neurochimie, 5, rue Blaise Pascal, F–67084 Strasbourg (FR). SCHMITT, Gaby [FR/FR]; Centre de Neurochimie, 5, rue Blaise Pascal, F–67084 Strasbourg (FR). KEYLING, Florence [FR/FR]; Centre de Neurochimie, 5, rue Blaise Pascal, F–67084 Strasbourg (FR). GIRLANDA, Céline [FR/FR]; Centre de Neurochimie, 5, rue Blaise Pascal, F–67084 Strasbourg (FR). YAMADA, Masashi [JP/JP]; Meiji Milk Products Co., Ltd., Nutritionals & Pharmaceuticals Development Dept., 26–11, Midori 1–chome, Sumida–ku, Tokyo 130–0021 (JP). SUMA, Yukie [JP/JP]; Meiji Milk Products Co., Ltd., Nutritionals & Pharmaceuticals Development Dept., 26–11, Midori 1–chome, Sumida–ku, Tokyo 130–0021 (JP).

(74) Agents: ARUGA, Mitsuyuki et al.; Kyodo Building, 3–6, Nihonbashiningyocho 1–chome, Chuo–ku, Tokyo 103–0013 (JP).

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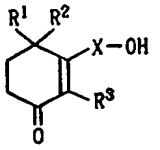

(1)

(57) Abstract

Described is a cyclohexenone long–chain alcohol represented by formula (1), wherein R1, R2 and R3 each independently represents a hydrogen atom or a methyl group and X represents a C10–18 alkylene or alkenylene group. The cyclohexenone long–chain alcohol according to the present invention has excellent neurite growth stimulating effects and is therefore useful as a preventive and/or therapeutic agent for Alzheimer's disease.

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DESCRIPTION

CYCLOHEXENONE LONG-CHAIN ALCOHOL AND MEDICAMENT CONTAINING SAME

Technical Field

The present invention relates to a cyclohexenone long-chain alcohol having excellent neurite growth stimulating effects which is useful as a preventive and/or therapeutic for cerebral diseases typified by dementia, and also as a medicament containing the same.

Background Art of the Invention

Nerve growth factors (which will hereinafter be abbreviated as "NGF"s), many of which exist primarily in the hippocampus and cerebral cortex, are neurotrophic factors which stimulate differentiation or growth of neurocytes and are therefore essential for maintenance of function and survival. They act on catecholamine activating neurons in the peripheral nervous system, as well as on cholinergic neurons in the brain. Alzheimer's disease is thought to have, as its main lesion, degeneration and defluxion of cholinergic neurons. Therefore there has been an attempt to administer NGFs into the brain for the treatment of Alzheimer's disease. NGFs, however, cannot pass through the blood-brain barrier because they are proteins having molecular weights as high as 12,000. Therefore such

treatment has not proven practical as a therepeutic method for humans. If there existed a low-molecular-weight compound which exhibited NGF-like effects and could pass through the blood-brain barrier or a compound capable of enhancing NGF synthesis in the brain, such a compound would likely be therapeutically useful for treating Alzheimer's disease. Based on this idea, substances exhibiting NGF-like effects have been sought. As a result, it has been shown that long-chain alcohols such as n-hexacosanol induce *in vitro* production of NGFs in gliacytes, thereby promoting neurite growth. In addition they can pass through the blood-brain barrier *in vivo* (Japanese Patent Application Laid-Open No. HEI 4-502167).

Effects of n-hexacosanol, however, have not been satisfactory yet.

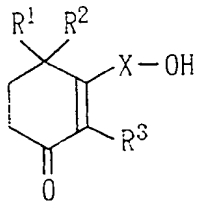
An object of the present invention is therefore to provide a medicament comprising a compound which can be orally administered, which readily transfers into the brain, and which permits neurite growth in the brain even at low concentrations compared with those of the above-described long-chain alcohols such as n-hexacosanol.

Disclosure of the present invention

Focusing on the skeletal structure of cyclohexenone, the present inventors synthesized a number of cyclohexane derivatives. As a result, it has been found that a

cyclohexenone long-chain alcohol represented by the below-described formula (1) is useful as a medicament for the prevention and treatment of cerebral diseases such as dementia because it has excellent neurite growth promoting effects even at lower concentrations compared with those of n-hexacosanol and has the effect of acting directly on the neurite, thereby stimulating neurite growth without inducing NGF production in gliacytes, leading to the completion of the present invention.

In one aspect of the present invention, there is thus provided a cyclohexenone long-chain alcohol represented by the following formula (1):



(1)

wherein R^1, R^2 and R^3 each independently represents a hydrogen atom or a methyl group and X represents a C_{10-18} alkylene or alkenylene group.

In another aspect of the present invention, there is also provided a medicament comprising as an effective ingredient the compound represented by the formula (1).

In a further aspect of the present invention, there is also provided a neurite growth stimulating agent comprising the compound represented by the formula (1) as an effective ingredient.

In a further aspect of the present invention, there is provided a pharmaceutical composition comprising the compound represented by the formula (1) and a pharmaceutically acceptable carrier.

In a further aspect of the present invention, there is provided use of the compound represented by the formula (1) as a medicament.

In a further aspect of the present invention, there is provided a method for the treatment of dementia comprising administering to a patient an effective amount of the compound represented by the formula (1).

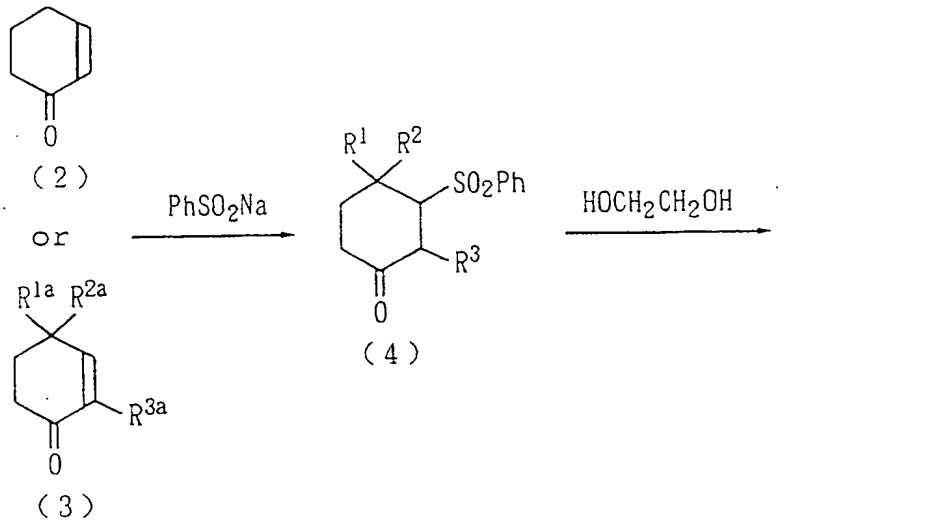
Best Modes for Carrying Out the Invention

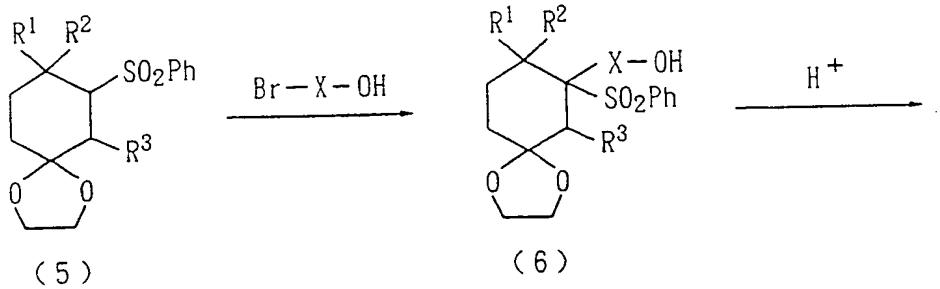
In the formula (1), among the C_{10-18} alkylene and alkenylene groups represented by X, preferred are C_{10-18} alkylene groups, with C_{10-16} alkylene groups being more preferred. For the alkylene or alkenylene group, either linear or branched one can be employed, with the linear one being more preferred. R^1, R^2 and R^3 each independently represents a hydrogen atom or a methyl group, with the case where at least one of them represents a methyl group being more preferred.

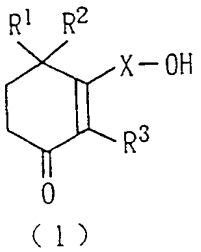
The compound of the present invention may exist in the form of a hydrate. The compound of the present invention has various isomers and these isomers are also embraced by the present invention.

The compound (1) of the present invention can be prepared, for example, in accordance with the following reaction processes A or B.

[Process A]







wherein R^{1a}, R^{2a} and R^{3a} each independently represents a hydrogen atom or a methyl group, with the proviso that at least one of them represents a methyl group, Ph represents a phenyl group and R1, R2 and R3 have the same meanings as defined above.

Described specifically, the invention compound (1) can be obtained by reacting cyclohexenone (2) or methyl-substituted-2-cyclohexen-1-one (3) with a benzenesulfinic acid salt in the presence of an acid to obtain Compound (4), reacting the resulting Compound (4) with ethylene glycol to obtain its ketal derivative (5), reacting the resulting derivative (5) with a ω-halogenoalkanol or ω-halogenoalkenol to obtain Compound (6), followed by subjecting Compound (6) to an acid treatment to eliminate the protective group.

The methyl-substituted-2-cyclohexen -1-one (3) used here as a raw material is available by reacting methyl-substituted cyclohexanone with a trialkylsilyl halide in the presence of butyl lithium, followed by oxidation in the presence of a palladium catalyst.

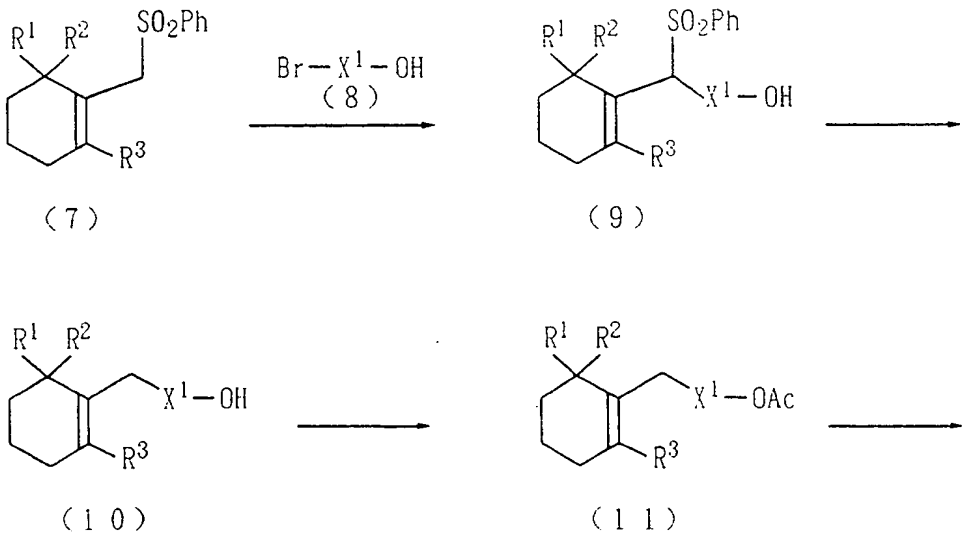
In the above reaction, the reaction between cyclohexanone (2) or methyl-substituted -2-cyclohexen-1-one (3) and a benzenesulfinic acid salt, for example, benzenesulfinic acid sodium is preferably effected in the presence of an acid such as hydrochloric acid, sulfuric acid or phosphoric acid at 0 to 100°C for 5 to 40 hours.

The reaction between Compound (4) and ethylene glycol is preferably carried out in the presence of a condensing agent such as paratoluenesulfonic anhydride at 50 to 120°C for 1 to 10 hours.

As a ω-halogenoalkanol to be reacted with the ketal derivative (5), a ω-bromoalkanol is preferred. It is desirable that the reaction between the ketal derivative (5) and a ω-bromoalkanol be carried out in the presence of a metal compound such as butyl lithium under low-temperature conditions.

The elimination of the phenylsulfonyl and ketal-protective groups from Compound (6) is preferably effected by reacting Compound (6) with an acid such as paratoluenesulfonic acid.

[Process B]



(7) (9) (10) (11)

(12) (1a)

wherein X1 represents C_{9-17} alkylene group or C_{9-17} alkenylene group, Ac represents an acyl group, R^1, R^2, R^3 and Ph have the same meanings as defined above.

Described specifically, compound (7) (obtained, for instance, through the method described in *Synthesis, 1996, Nov.*) is reacted with ω-bromoalcohol to obtain compound (9), subsequently the phenylsulphonyl group of the resulting compound being eliminated to give compound (10), followed by protection of the hydroxy group of compound (10) to yield compound (11). The resulting compound is subsequently oxidized to obtain compound (12), and the hydroxy-protective group of the resulting compound is then eliminated to obtain compound (12).

The reaction between compound (7) and compound (8) is preferably carried out at low temperatures in the presence of a metal compound such as butyl lithium.

The elimination of the phenylsulphonyl group from compound (9) may be conducted by reacting the compound and a phosphate in the presence of sodium amalgam.

As a hydroxy-protective group of compound (10), the acetyl group is preferred, the protection reaction being

preferably performed, for example, by reacting compound (10) and acetic anhydride.

The oxidation reaction of compound (11) may preferably be performed by reacting the compound and an alkyl hydroperoxide such as t-butyl hydroperoxide in the presence of a metal compound such as ruthenium trichloride.

The elimination reaction of the protective group of compound (12) is preferably performed by hydrolyzing the compound in the presence of a base such as potassium carbonate.

Since the invention compound (1) so obtained has excellent neurite growth stimulating effects and is capable of passing through the blood-brain barrier owing to its low molecular weight, it is useful as a preventive and/or therapeutic for diseases caused by neural degeneration and defluxion, for example, dementia typified by Alzheimer's disease.

The medicament according to the present invention can be administered either through an oral route or a parenteral (such as intramuscular, subcutaneous, intravenous or suppository) route. Also, the medicament can be administered in the form of a composition comprising compound (1) and a pharmaceutically acceptable carrier.

Oral preparations can be formulated into tablets, covered tablets, granules, capsules, solutions, syrups, elixirs, oil or aqueous suspensions in a manner known *per*

se in the art after the addition of an excipient and if necessary a binder, a disintegrator, a lubricant, a colorant and/or a corrigent. Examples of the excipient include lactose, corn starch, sucrose, glucose, sorbitol and crystalline cellulose. Examples of the binder include polyvinyl alcohol, polyvinyl ether, ethyl cellulose, methyl cellulose, gum arabic, tragacanth, gelatin, shellac, hydroxypropyl cellulose, hydroxypropyl starch and polyvinyl pyrrolidone.

Examples of the disintegrator include starch, agar, gelatin powder, crystalline cellulose, calcium carbonate, sodium bicarbonate, calcium citrate, dextran and pectin; those of the lubricant include magnesium stearate, talc, polyethylene glycol, silica and hardened vegetable oil. As the colorant, pharmaceutically acceptable colorants can be used. Examples of the corrigent include cocoa powder, menthol, aromatic acid, peppermint oil, camphor and cinnamon powder. The tablet can also be used in the form of a coated tablet available by applying sugar coating, gelatin coating or the like to granules as needed.

Injections, more specifically, subcutaneous, intramuscular and intravenous injections are formulated in a manner known *per se* in the art by adding a pH regulator, buffer, stabilizer and/or preservative as needed. It is also possible to fill the injection solution in a vial or the like and lyophilize it into a solid preparation which is

reconstituted immediately before use. One dose is filled in a vial or alternatively, multiple doses are filled in one vial.

For human adult, the dose of the medicament according to the present invention falls within a range of from 0.01 to 1000 mg/day, with a range of from 0.1 to 100 mg/day being preferred. For animals, on the other hand, the dose falls within a range of from 0.01 to 1000 mg. preferably 0.1 to 100 mg per kg of the animal to be treated. This daily dose is administered once a day or in 2 to 4 portions a day.

Examples

The present invention will hereinafter be described by examples, but it should however be borne in mind that the present invention is not limited to or by these examples.

Example 1

(1) Benzenesulfinic acid sodium salt (10.25 g) was added to a solution containing 5 ml of cyclohexenone and 30 ml of water, followed by the dropwise addition of 60 ml of 1N hydrochloric acid. The reaction mixture was stirred at room temperature for 24 hours. The crystals so precipitated were filtered and then washed with water, isopropanol and cold ethyl ether. After recrystallization from isopropanol, 5.74 g of 3-(phenylsulfonyl)-cyclohexan-1-one were obtained in the form of white crystals. Yield: 97%

3-(Phenylsulfonyl)-cyclohexan-1-one

Molecular weight: 238 ($C_{12}H_{14}O_3S$)

Melting point: 83 to 85°C

TLC: (hexane-AcOEt: 6-4) Rf=0.2

^{1}H NMR (200 MHz, $CDCl_3$), δ:1.53-1.77 (m,2H,H-5); 2.1-2.45 (m, 4H,H-4,6); 2.6 (d,J=9.1Hz,2H,H-2); 3.2-3.4 (m,1H,H-3);7.5-7.7 (m,3H,H ar.-3',4'); 7.8-7.9 (m,2H,H ar.-2').

^{13}C NMR (50 MHz, $CDCl_3$), δ:23.2(C-5*); 23.5(C-4*);40.1(C-6°); 40.2(C-2°); 62.1(C-3); 128.8(C ar.-2'); 129.3(C ar.-3'); 134(C ar.-4'); 136.5(C ar.-1'); 206.2(C-1).

IR(KBr):3053,2966,2926,1708,1582,1450,1304,1288,1228,1198,1159,1138,1084,1062,912,765,728,693,661,605,540.

UV(acetonitrile):λmax:222nm(ε3740), λ:258(ε640),264(ε905),271(ε777).

MS(El):238.1(M^+,0.3); 143($PhSO_2H_2$,0.2); 141($PhSO_2$,0.3); 125(PhSO,0.4); 120.1($(CH_2)_4SO_2$,0.4); 110(PhSH,0.3);97 (M-$PhSO_2$,0.3); 125(PhSO,0.4); 120.1 ($(CH_2)_4SO_2$,0.4); 110 (PhSH,0.3)97(M-$PhSO_2$,100); 96(cyclohexene, 17); 77(Ph,19); 69.1($(CH_2-)_3$-CH=CH_2,63.2); 55.1($(CH_2-)_2$-CH=CH_2,22).

Analysis (%):calculated C:60.5,H:5.9;found C:60.4,H:5.7.

(2) To a solution of 5.3 g of 3-(phenylsulfonyl)-cyclohexan-1-one in 60 ml of benzene, were added 0.3 ml of 1,2-ethanediol and 0.2 g of anhydrous paratoluenesulfonic acid. The reaction mixture was heated under reflux for 4 hours. After the reaction, a 2M aqueous sodium bicarbonate solution was added and the resulting mixture was extracted with ethyl acetate three times. The combined organic layers

were washed with saturated saline and then, dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was recrystallized from ethyl ether, whereby 6.1 g of 1,1-(ethylenedioxy)-3-(phenylsulfonyl)-cyclohexane were obtained in the form of white crystals. Yield: 97%

1,1-(Ethylenedioxy)-3-(phenylsulfonyl)-cyclohexane

Molecular weight: 282 ($C_{14}H_{18}O_4S$)

Melting point: 93 to 95°C

TLC: (hexane-AcOEt: 6-4) Rf=0.26

^{1}H NMR (200 MHz, $CDCl_3$), δ :1.3-1.6 (m,3H,H-5,4a); 1.61(t,J=12.5Hz,1H,H-2a); 1.65-1.73(m,1H,H4c);1.75-2.05(m,2H,H6);2.12(ddt,J_{gem}=12.5Hz,^{3}J=3.5Hz,^{4}J=2.5Hz,1H,H-2c); 3.21(tt,^{3}J=12.5Hz,^{3}J=3.5Hz,1H,H-3); 3.84-3.99 (m,4H,O-CH_2-CH_2-O); 7.5-7.7(m,3H,H ar.-3',4'); 7.8-7.9(m,2H,H ar.-2').

^{13}C NMR (50 MHz, $CDCl_3$), δ :21.8(C-5); 24.5(C-4); 33.9(C-2*); 34.1(C-6*); 61.3(C-3); 64.4(O-$\underline{C}H_2$-$\underline{C}H_2$-O); 107.9(C-1); 128.9(C ar.-2'°); 129(C ar.-3'°); 133.6(C ar.-4'); 136.9(C ar.-1').

IR(KBr):3060,2968,2938,2894,1583,1448,1301,1267,1158,1144,1082,1023,939,916,838,749,718,689.

UV(acetonitrile):λmax:222nm(ε 4970),λ:258(ε 710),264(ε 1010),271(ε 861).

MS(Cl,NH_3):300.2(MNH_4^+,100);283.1(MH^+,27);256.1(8);141.1(M-SO_2Ph,83).

Analysis (%):calculated C:59.82,H:6.32;found C:59.6,H:6.4.

(3) A solution of n-butyl lithium (2 ml) was added dropwise to a solution of 565 mg of 1,1-(ethylenedioxy)-3-(phenylsulfonyl)-cyclohexane and 4 mg of triphenylmethane in 5 ml of THF at -78°C under an argon gas stream. After stirring for 10 minutes, the reaction was effected at room temperature for 1 hour. HMPT (1 ml) was added. The solution was stirred at room temperature for 1 hour after recooling to -78°C. A solution of 159 mg of 10-bromo-1-decanol in 2 ml of THF was added dropwise to the reaction mixture.

After reaction at -20°C for 2 hours, the reaction mixture was poured into a saturated solution of ammonium chloride. The resulting mixture was extracted with ethyl ether. The organic layer was washed with water and saturated saline and then, dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column while using hexane-ethyl acetate, whereby 265 mg of 1,1-(ethylenedioxy)-3-(10-hydroxydecyl)-3-(phenylsulfonyl)-cyclohexane were obtained in the form of a colorless oil.

Yield: 90%

1,1-(Ethylenedioxy)-3-(10-hydroxydecyl)-3-(phenylsulfonyl)-cyclohexane

Molecular weight: 438 ($C_{24}H_{38}O_5S$)

TLC: (hexane-AcOEt: 6-4) Rf=0.14

^{1}H NMR (200 MHz, $CDCl_3$), δ:1.26 (s large,14H,H-8 a H-14);1.57(q large,^{3}J=6.5Hz,2H,H-15);1.6-1.94(m,8H,H-4,5,6,7);1.98(s,2H,H-2);3.64 (t,J=6.5 Hz,2H,H-16);3.86-3.92(m,4H,O-CH_2-CH_2-O);7.5-7.7 (m,3H,H ar.-3',4');7.81-7.87 (m,2H,H ar.-2').

^{13}C NMR (50 MHz, $CDCl_3$), δ:19(C-5);23.8(C-14);25.7(C-7);28.4(C-4);29.5(C-10 a C-13);30.2(C-8);30.5(C-9);32.7(C-15); 34.5(C-6);35.7(C-2);62.9(C-16); 63.8,64.8(O-CH_2-CH_2-O);67.4(C-3);108.5(C-1);128.7(C ar.-3'*);130.3(C ar.-2'*);133.5(C ar.-4');135.8(C ar.-1').

IR(NaCl):3510,3063,2926,2853,1585,1447,1286,1140,1096,1083,723,693.

UV(acetonitrile): λmax:218nm(ε 8600), λ:258(ε 1050),265(ε 1300),271(ε 1150).

MS(IC-NH_3): 456.3(MNH_4^+,36);439.2(MH^+,3.5);299.3(MH_2-SO_2Ph,33);297.2(M-SO_2Ph,100);141(SO_2Ph,10);98.9($C_6H_{11}O$,28).

(4) Paratoluenesulfonic acid (20 mg) was added to a solution of 193 mg of 1,1-(ethylenedioxy)-3-(10-hydroxydecyl)-3-(phenylsulfonyl)-cyclohexane in 3 ml of chloroform and 0.6 ml of acetone. To the resulting mixture was added 10 ml of a saturated aqueous solution of sodium bicarbonate, followed by extraction with dichloromethane. The organic layer was washed with saturated saline and dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by

chromatography on a silica gel column using hexane-ethyl acetate, whereby 86 mg of 3-(10-hydroxydecyl)-2-cyclohexen-1-one were obtained in the form of a colorless oil. Yield: 77%

3-(10-Hydroxydecyl)-2-cyclohexan-1-one

Molecular weight 252 ($C_{16}H_{28}O_2$)

TLC: (hexane-AcOEt: 6-4) Rf=0.33

^{1}H NMR (200 MHz, $CDCl_3$), δ :1.28 (s large,14H,H-8 a H-14);1.44-1.59(m,2H,H-15);1.97(q.J=6.4 Hz,2H,H-5);2.1-2.4(m,6H,H-4,6,7);3.64 (t,J=6.4 Hz,2H,H-16);5.87 (s,1H,H-2).

^{13}C NMR (50 MHz, $CDCl_3$), δ :22.6(C-5);25.6(C-14);26.8(C-4);29.3(C-8 to C-13);32.6(C-15);37.2(C-7);37.9(C-6);62.7(C-16);125.5(C-2);166.9(C-3);200.1(C-1).

IR(NaCl):3446,3058,2926,2854,1665,1624,1446,1301,1152,1125,1078,728,693.

UV(acetonitrile): λmax:232nm(ε 16050).

MS(El):252.1(M^+,9);222.1(8);124(12);123($C_8H_{11}O$,93);110(100);97(C_6H_9O,65);95(C_6H_7O,22);82(64);81(13);79(12);66.9(26);55(23).

Analysis (%):calculated C:79.14,H:11.18;found: C:75.8,H:10.9.

Example 2

In a similar manner to Example 1, 3-(11-hydroxy-undecyl)-2-cyclohexen-1-one was obtained.

Molecular weight: 266 ($C_{17}H_{30}O_2$)

TLC: (hexane-AcOEt: 6-4) Rf=0.2

Melting point: 34 to 35°C

MS(El):266.1(M^+,9); 248.1(M-H_2O,2); 236.1(8); 124(11); 123($C_8H_{11}O$,83);109.9(100);97(56);95(C_6H_7O,25);82(51);81(13);79(12);69(7);66.9(23);55(21).

Analysis (%):

calculated C:76.64,H:11.35;

found:C:76.4 H:11.6.

Example 3

In a similar manner to example 1, 3-(12-hydroxydodecyl)-2-cyclohexen-1-one was obtained.

Molecular weight: 280 ($C_{18}H_{32}O_2$)

TLC: (hexane-AcOEt: 6-4) Rf=0.24

Melting point: 35 to 36°C

MS(El):280.3(M^+,12); 262.1(M-H_2O,3); 250.1(7); 150.9($C_{10}H_{15}O$,5); 136.9($C_9H_{13}O$,4); 124(10); 123($C_8H_{11}O$,84); 110(100); 97(51); 95(C_6H_7O,22); 82(46); 81(10); 78.9(10); 66.9(20); 55(22).

Analysis (%):

calculated C:77.07,H:11.50

found:C:77.1 H:11.5.

Example 4

In a similar manner to Example 1, 3-(13-hydroxytridecyl)-2-cyclohexen-1-one was obtained.

Molecular weight: 294 ($C_{19}H_{34}O_2$)

TLC: (hexane-AcOEt: 6-4) Rf=0.26

Melting point: 42 to 43°C

MS(El):294.2(M^+,8); 276.1(M-H_2O,2); 264.1(5); 151($C_{10}H_{15}O$,5); 136.9($C_9H_{13}O$,4); 124(9); 123($C_8H_{11}O$,77); 111(8); 109.9(100); 97(46); 95(C_6H_7O,20); 82(36); 81.1(10); 78.9(8); 66.9(18); 55(21).

Analysis (%):

calculated C:77.50 H:11.64

found:C:77.4 H:11.5.

Example 5

In a similar manner to Example 1, 3-(14-hydroxy-tetradecyl)-2-cyclohexen-1-one was obtained.

Molecular weight: 308 ($C_{20}H_{36}O_2$)

TLC: (hexane-AcOEt: 6-4) Rf=0.28

Melting point: 44 to 45°C

MS(El):308.1(M^+,10); 290.3(M-H_2O,3); 278.4(6); 150.9($C_{10}H_{15}O$,5); 137($C_9H_{13}O$,3); 124(8); 123($C_8H_{11}O$,77); 111(8); 109.9(100); 97(44); 95(C_6H_7O,19); 82(30); 81.1(8); 78.9(7); 66.9(18); 55(20).

Analysis (%):

calculated C:77.87 H:11.76

found:C:77.6 H:11.4.

Example 6

(1) A 1.4M n-butyl lithium solution (35.4 ml) was added dropwise to a solution of 7 ml of N,N-diisopropylamine in 20 ml of THF at -78°C. The resulting mixture was stirred at 0°C for 30 min. Four ml of 4-methylcyclohexan-1-one in

10 ml of THF at -78° C was added dropwise to the LDA solution. After stirring at -78° C for 1 hour, 6.5 ml of trimethylsilyl chloride were added to the reaction mixture. The resulting mixture was stirred at room temperature for 1 hour and then poured into an aqueous solution of sodium bicarbonate, followed by extraction with ethyl ether. The organic layer was washed with saturated saline and dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by distillation under reduced pressure, whereby 5.83 g of 4-methyl-1-(trimethylsilyloxy)-1-cyclohexene were obtained. Yield: 96%

4-Methyl-1-(trimethylsilyloxy)-1-cyclohexene

Molecular weight: 184 ($C_{10}H_{20}OSi$)

TLC: (hexane-AcOEt: 8-2) Rf=0.8

^{1}H NMR (200 MHz, $CDCl_3$), δ :0.17 (s,9H,Si-$(CH_3)_3$); 0.94(d.J=6.2 Hz,3H,H-7);1.2-1.43(m,1H,H-4);1.57-1.76 (m,3H,H-3.6); 1.88-2.14 (m,3H,H-5); 4.8-4.83 (m,1H,H-2).

^{13}C NMR (50 MHz, $CDCl_3$), δ :0.3(Si-$(CH_3)_3$);21.2(C-7);28.3(C-4);29.6(C-5);31.3(C-6);32.3(C-3);103.5(C-2);150.1(C-1).

IR(NaCl):3052,3021,2954,2926,1670,1457,1371,1252,1190,1046,892,844.

(2) A catalytic amount of palladium (II) acetate was added to a solution of 3.53 g of 4-methyl-1-(trimethylsilyloxy)-1-cyclohexene in 70 ml of DMSO, followed by stirring while introducing oxygen for 6 hours.

After the addition of water at 0°C, the reaction mixture was filtered over celite and then extracted with ethyl ether. The solvent was distilled off under reduced pressure and the residue was dissolved in hexane-water. The resulting solution was extracted with hexane. The hexane layer was washed with saturated saline and dried over magnesium sulfate. The solvent was distilled off under reduced pressure, whereby 4-methyl-2-cyclohexen-1-one was obtained in the form of an oil. Yield: 72%

4-Methyl-2-cyclohexen-1-one

Molecular weight: 110 ($C_7H_{10}O$)

TLC: (hexane-AcOEt: 8-2) Rf=0.35

^{1}H NMR (200 MHz, $CDCl_3$), δ :1.15 (d,J=7.1 Hz,3H,H-7); 1.56-1.76(m,1H,H-5a);2.1(dqa,J_{gem}=13.3 Hz, ^{3}J=4.9 Hz,1H,H-5e);2.26-2.48(m,2H,H-6);2.49-2.62 (m,1H,H-4); 5.94 (dd, ^{3}J=10.1 Hz, ^{4}J=2.5 Hz,1H,H-2);6.79 (ddd, ^{3}J=10.1 Hz, ^{3}J=2.7, ^{4}J=1.5 Hz,1H,H-3).

^{13}C NMR (50 MHz, $CDCl_3$), δ :20.1(C-7);29.6(C-5);30.9(C-4);36.8(C-6);128.4(C-2);156.2(C-3);199.7(C-1).

IR(NaCl):3025, 2958, 2932, 1683, 1617, 1458, 1391, 1375, 1251, 1094, 1053, 1016, 828, 750.

(3) Benzenesulfinic acid sodium salt (3.0 g) was added to a solution containing 1.52 g of 4-methyl-2-cyclohexen-1-one and 9 ml of water. 1N Hydrochloric acid (18 ml) was added dropwise to the resulting solution. After stirring at room temperature for 24 hours, the crystals so

precipitated were filtered and washed with water, isopropanol and cold ethyl ether. After recrystallization from isopropanol, 4-methyl-3-(phenylsulfonyl)-cyclohexan-1-one was obtained in the form of white crystals.

Yield: 72%

4-Methyl-3-(phenylsulfonyl)-cyclohexan-1-one

Molecular weight: 252 ($C_{13}H_{16}O_3S$)

Melting point: 71 to 74°C

TLC* (hexane-AcOEt: 6-4) Rf=0.2

^{1}H NMR (200 MHz, $CDCl_3$),

-trans: δ :1.32 (d, J=6.9 Hz,3H,H-7); 1.5-1.7 (m, 1H,H-5); 2.15-2.3(m,1H,H-5); 2.35-2.5 (m,3H,H-4.6);2.55-2.68 (m,2H,H-2); 3.17(ddd,J=8 Hz,J=6.6 Hz,J=6.4 Hz,1H,H-3); 7.52-7.72(m,3H,H ar.-3',4'); 7.83-7.9(m,2H,H ar.-2').

-cis: δ :1.44 (d, J=7.1 Hz,3H,H-7); 1.75-1.9 (m, 1H,H-5); 1.95-2.1(m,1H,H-5); 2.35-2.5 (m,3H,H-4.6);2.73-2.9 (m,2H,H-2); 3.34(dt,J=12.9 Hz,J=4 Hz,1H,H-3); 7.52-7.72(m,3H,H ar.-3',4'); 7.83-7.9(m,2H,H ar.-2').

^{13}C NMR (50 MHz, $CDCl_3$),

-trans: δ :20.3(C-7); 28.5(C-4);30.4(C-5); 37.9(C-6*); 38.6(C-2*); 66.3(C-3); 128.6(C ar.-2^{10}); 129.1(C ar.-3^{10}); 133.9(C ar.-4'); 137.2(C ar.-1');206.1(C-1).

-cis: δ :13(C-7); 27.2(C-4);31.1(C-5); 35.9(C-6*); 36.9(C-2*); 64.6(C-3); 128.3(C ar.-2^{10}); 129.1(C ar.-3^{10}); 133.9(C ar.-4'); 138(C ar.-1');206.6(C-1).

MS(El):111.1(M-SO_2Ph,88); 110.1(27); 83.15(32); 77.1(29); 69.1(36); 55.2(100).

(4) To a solution of 2.45 g of 4-methyl-3-(phenylsulfonyl)-cyclohexan-1-one in 40 ml of benzene, were added 0.7 ml of 1,2-ethanediol and 0.2 g of anhydrous paratoluenesulfonic acid. The resulting mixture was heated under reflux for 4 hours. After the reaction, a 2M aqueous sodium bicarbonate solution was added and the resulting mixture was extracted with ethyl acetate three times. The combined organic layers were washed with saturated saline, and dried over magnesium sulfate. The solvent was then distilled off under reduced pressure. The residue was recrystallized from ethyl ether, whereby 1,1-(ethylenedioxy)-4-methyl-3-(phenylsulfonyl)-cyclohexane was obtained in the form of white crystals. Yield: 97%

Molecular weight: 296 ($C_{15}H_{20}O_4S$)

Melting point: 105 to 106°C

TLC: (hexane-AcOEt: 6-4) Rf=0.3

^1H NMR (200 MHz, $CDCl_3$),

-<u>trans</u>: δ:1.23 (d, J=6.1 Hz,3H,H-7); 1.37-1.77 (m, 6H,H-2a,4,5,6); 1.84(ddd,J_{gem}=12.9 Hz,^3J=3.7 Hz,^4J=2.7 Hz,1H,H-2e); 3.02 (ddd,^3J=13 Hz,^3J=10.3 Hz, ^3J=3.7 Hz,1H,H-3);3.71-3.91(m,4H,O-CH_2-CH_2-O); 7.48-7.67(m,3H,H ar.-3',4'); 7.8-7.88(m,2H,H ar.-2').

-<u>cis</u>: δ:1.18 (d, J=6.9 Hz,3H,H-7); 1.37-1.77 (m,4H,H-5.6); 7.84(ddd,J_{gem}=13 Hz,^3J=3.7 Hz,^4J=2.7 Hz,1H,H-2e); 2.02

(t,J=13 Hz,1H,H-2a);2.30-2.45 (m,1H,H-4); 3.29(dt,^{3}J=13 Hz,^{3}J=3.7 Hz,1H,H-3); 3.71-3.91(m,4H,O-CH_2-CH_2-O); 7.48-7.67(m,3H,H ar.-3',4'); 7.8-7.88(m,2H,H ar.-2').

^{13}C NMR (50 MHz, $CDCl_3$),

-<u>trans</u>: δ :20.4(C-7); 31.9(C-4);32.6(C-5); 34.1(C-6); 35.8(C-2); 64.4(CH_2-O); 66.8(C-3); 107.9(C-1); 128.6(C ar.-3'*); 129(C ar.-2'*);133.5(C ar.-4');138(C ar.-1').

-<u>cis</u>: δ :12.4(C-7); 26.7(C-4);29.2(C-5.6); 32(C-2); 64.1(C-3); 64.4(CH_2-O); 108.2(C-1); 128.3(C ar.-2',3'); 133.5(C ar.-4'); 138.5(C ar.-1').

IR(KBr): 3060, 2968, 2938, 1583, 1448, 1301, 1267, 1158, 1144, 1082, 1023, 939, 916, 838, 749, 718, 689.

Analysis (%): calculated $C_{15}H_{20}O_4S$(296.4)C:60.79, H:6.8; found: C60.5, H:6.9

(5) A solution of n-butyl lithium (1.8 ml) was added dropwise to a solution of 560 mg of 1,1-(ethylenedioxy)-4-methyl-3-(phenylsulfonyl)-cyclohexane and 4 mg of triphenylmethane in 5 ml of THF under an argon stream at -78° C. The resulting mixture was stirred for 10 minutes and then reacted at room temperature for 1 hour. HMPA (1 ml) was added and the resulting mixture was recooled to -78° C, followed by the dropwise addition of a solution of 166 mg of 10-bromo-1-decanol in 2 ml of THF. After stirring the reaction at -20° C for 2 hours, the reaction mixture was poured into a saturated solution of ammonium chloride. The resulting mixture was extracted with ethyl ether. The organic layer

was washed with water and saturated saline and then, dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column while using hexane-ethyl acetate, whereby 1,1-(ethylenedioxy)-3-(10-hydroxydecyl)-4-methyl-3-(phenylsulfonyl)-cyclohexane was obtained in the form of a colorless oil. Yield: 97%

1-1-(Ethylenedioxy)-3-(10-hydroxydecyl)-4-methyl-3-(phenylsulfonyl)-cyclohexane

Molecular weight: 452 ($C_{25}H_{40}O_5S$)

TLC: (hexane-AcOEt: 6-4) Rf=0.14

^{1}H NMR (200 MHz, $CDCl_3$), δ :1.13 (d,j=6 Hz,3H,H-17); 1.28(s large,12H,H-9a,H-14); 1.43-1.6(m,9H,H-4,5,6,7,8,15); 1.67(m,1H,H-2); 1.89(dd,J_{gem}=12.5Hz,J=3.5 Hz,1H,H-6e); 2.14(t large,J=12.5 Hz,1H,H-6a); 2.43(dd,J_{gem}=13.8 Hz,^{4}J=2.5 Hz,1H,H-2); 3.63(t,J=6.5 Hz,2H,H-16); 3.83-3.97(m,4H,O-CH_2-CH_2-O);7.49-7.68(m,3H,H ar.-3',4'); 7.8-7.88(m,2H,H ar.-2').

^{13}C NMR (50 MHz, $CDCl_3$), δ :16.1(C-17); 24.4(C-14); 25.6(C-5*); 25.8(C-7*); 29.5(C-9 a C-13); 30.3(C-8); 32.7(C-15); 34.9(C-6); 35.5(C-4); 36.2(C-2); 32.8(C-16);63.9,65.1(O-CH_2-CH_2-O); 71.2(C-3); 108.4(C-1); 128.7(C ar.-3'); 130.1(C ar.-2'); 133.3(C ar.-4'); 136.8(C ar.-1').

IR(KBr):3510, 3063, 2926, 2853, 1584, 1286, 1140, 1096, 1083.

MS(Cl-NH_3): 470.3(MNH_4^+,2); 313.3(MH_2-SO_2Ph,23); 312.3(MH-SO_2Ph,19); 311.2(M-SO_2Ph,100); 255.1(19); 155(5); 99(59); 81(5); 78(9).

(6) Paratoluenesulfonic acid (20 m) was added to a solution of 235 mg of 1,1-(ethylenedioxy)-3-(10-hydroxydecyl)-4-methyl-3-(phenylsulfonyl)-cyclohexane in 20 ml of chloroform and 4 ml of acetone. The resulting mixture was reacted at 50°C for 24 hours. To the reaction mixture were added 10 ml of a saturated aqueous solution of sodium bicarbonate, followed by extraction with dichloromethane. The organic layer was washed with saturated saline and dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column while using hexane-ethyl acetate, whereby 3-(10-hydroxydecyl)-4-methyl-2-cyclohexen-1-one was obtained in the form of a colorless oil. Yield: 75%

3-(10-Hydroxydecyl)-4-methyl-2-cyclohexen-1-one

Molecular weight: 266 ($C_{17}H_{30}O_2$)

CCM: (hexane-AcOET: 6-4) Rf=0.2

^{1}H NMR (200 MHz, $CDCl_3$), δ :1.18 (d,J=7.1 Hz,3H,H-17); 1.27(s large,12H,H-9 to H-14); 1.40-1.57(m,4H,H-8,15); 1.76(dqa,J_{gem}=13.3 Hz,J=5.8 Hz,1H,H-5e); 2.01-2.13(m,1H,H-5a); 2.15-2.26 (m,2H,H-7); 2.28-2.56(m,3H,H-4,6); 3.63(t,J=6.4 Hz,2H,H-16); 5.8(s large,1H,H-2).

^{13}C NMR (50 MHz, $CDCl_3$), δ :17.6(C-17); 25.6(C-14); 26.9(C-5); 29.2(C-9 a C-13); 30(C-8); 32.6(C-15); 32.8(C-4); 34(C-7); 35.4(C-6); 62.6(C-16); 124.6(C-2); 170.7(C-3); 199.7(C-1).

IR(KBr):3450, 3058, 2926, 2854, 1665, 1624, 1055, 1043.

UV(acetonitrile): λmax:228nm(ε 10840).

MS(EI):266.1(M^+,31);248.1(M-H_2O,6); 236.1(21); 165($C_{11}H_{17}O$,8); 151($C_{10}H_{15}O$,5); 138(14); 137($C_9H_{13}O$,100); 123.9(98); 111(85); 110(21); 109(C_7H_9O,38); 96(56); 95(29); 82.1(11); 81(29); 78.9(15); 69(10); 67(29); 55(38).

Analysis (%):calculated $C_{17}H_{30}O_2$(266.4) C:76.64, H:11.35; found

C:76.5,H:11.5.

Example 7

In a similar manner to Example 6, 3-(11-hydroxy-undecyl)-4-methyl-2-cyclohexen-1-one was obtained.

Molecular weight: 280 ($C_{18}H_{32}O_2$)

TLC: (hexane-AcOET: 6-4) Rf=0.21

MS(EI):280.1(M^+,25);262.1(M-H_2O,7); 250.1(21); 165($C_{11}H_{17}O$,7); 151($C_{10}H_{15}O$,5); 138.1(13); 137($C_9H_{13}O$,100); 123.9(94); 111(86); 110(20); 109(C_7H_9O,41); 96(46); 95.1(26); 82.1(10); 81(28); 78.9(15); 69(12); 67(28); 55(35).

Analysis (%):

calculated C:77.09, H:11.50

found C:76.9,H:11.3

Example 8

In a similar manner to Example 6, 3-(12-hydroxydodecyl)-4-methyl-2-cyclohexen-1-one was obtained.

Molecular weight: 294 ($C_{19}H_{34}O_2$)

TLC: (hexane-AcOET: 6-4) Rf=0.22

MS(EI):294.1(M^+,29);276.1(M-H_2O,8); 364.1(21); 165($C_{11}H_{17}O$,7); 151($C_{10}H_{15}O$,4); 138.1(12); 137($C_9H_{13}O$,100); 123.9(88); 111(73); 110(17); 109(C_7H_9O,36); 96(37); 95.1(22); 82(9); 80.9(28); 78.9(13); 69(12); 67(25); 55(32).

Analysis (%):

calculated C:77.50, H:11.64

found C:77.2, H:11.5

Example 9

In a similar manner to Example 6, 3-(13-hydroxytridecyl)-4-methyl-2-cyclohexen-1-one was obtained.

Molecular weight: 308 ($C_{20}H_{36}O_2$)

TLC: (hexane-AcOET: 6-4) Rf=0.25

MS(EI):308.1(M^+,31);290.1(M-H_2O,10); 278.1(21); 164.9($C_{11}H_{17}O$,9); 151($C_{10}H_{15}O$,4); 138.1(12); 137($C_9H_{13}O$,90); 123.9(100); 111(73); 110(17); 109(C_7H_9O,40); 96(33); 94.9(26); 81(25); 79(13); 69(14); 67(23); 55(37).

Analysis (%):

calculated C:77.87, H:11.76

found C:77.6, H:11.5

Example 10

In a similar manner to Example 6, 3-(14-hydroxy-tretradecyl)-4-methyl-2-cyclohexen-1-one was obtained.

Molecular weight: 322 ($C_{21}H_{38}O_2$)

TLC: (hexane-AcOET: 6-4) Rf=0.3

MS(EI):322.2(M^+,37);304.1(M-H_2O,12); 292.1(21); 164.9($C_{11}H_{17}O$,9); 151($C_{10}H_{15}O$,4); 138.1(12); 137($C_9H_{13}O$,98); 123.9(100); 111(69); 110(17); 109(C_7H_9O,43); 96(30); 94.9(24); 81(24); 78.9(13); 69(15); 67(25); 55(37).

Analysis (%):

calculated C:78.20, H:11.88

found C:78.6, H:11.9

Example 11

(1) Benzenesulfinic acid sodium salt (5.98 g) was added to a solution containing 3 ml of 4,4-dimethyl-2-cyclohexen-1-one and 20 ml of water. Forty ml of 1N hydrochloric acid were added dropwise to the resulting mixture. The reaction mixture was stirred at room temperature for 24 hours. The crystals so precipitated were filtered and the solid, washed with water, isopropanol and cold ethyl ether. After recrystallization from isopropanol, 4,4-dimethyl-3-(phenylsulfonyl)-cyclohexan-1-one was obtained in the form of white crystals. Yield: 89%

4,4-Dimethyl-3-(phenylsulfonyl)-cyclohexan-1-one

Molecular weight: 206 ($C_{14}H_{18}O_3S$)

Melting point: 84 to 86°C

TLC: (hexane-AcOET: 6-4) Rf=0.3

^{1}H NMR (200 MHz, $CDCl_3$), δ :1.52 (s,6H,H7,8); 1.67(ddd,J_{gem}=14 Hz,^{3}J=12.3 Hz,^{3}J=4.4 Hz,1H,H-5a); 1.85(ddd,J_{gem}=14 Hz,^{3}J=6.2 Hz,^{3}J=4.4 Hz,1H,H-5e); 2.26(ddd,J_{gem}=15.5 Hz,^{3}J=4.6 Hz,^{4}J=2 Hz,1H,H-2e); 2.29(dtd,J_{gem}=15.7 Hz,^{3}J=4.4 Hz,^{4}J=2 Hz,1H,H-6e); 2.51(dddd,J_{gem}=15.7 Hz,^{3}J=12.3 Hz,^{3}J=6.2 Hz,^{4}J=1 Hz,1H,H-6a); 2.75(ddd,J_{gem}=15.5 Hz,^{3}J=12.2 Hz,^{4}J=1 Hz,1H,H-2a); 3.18(dd,^{3}J=12.2 Hz,^{3}J=4.6 Hz,1H,H-3); 7.52-7.7(m,3H,H ar.-3',4');7.82-7.88(m,2H,H ar.-2').

^{13}C NMR (50 MHz, $CDCl_3$), δ :21.3(C-7); 30(C-8); 34.8(C-4); 37.1(C-6); 38.9(C-2); 40.8(C-5); 69(C-3); 128.4(C ar.-2'*); 129.3(C ar.-3'*); 133.8(C ar.-4'); 139.1(C ar.-1');207.1(C-1).

Analysis(%): calculated $C_{14}H_{18}O_3S$(266.4) C:63.13, H:6.8; found:C:63, H:6.6

(2) To a solution obtained by dissolving 4.4 g of 4,4-dimethyl-3-(phenylsulfonyl)-cyclohexan-1-one in 45 ml of benzene, were added 1.1 nm of 1,2-ethanediol and 0.3 g of anhydrous paratoluenesulfonic acid. The resulting mixture was heated under reflux for 4 hours. After the reaction, a 2M aqueous sodium bicarbonate solution was added and the resulting mixture was extracted with ethyl acetate three times. The combined organic layers were washed with saturated saline and dried over magnesium sulfate. The solvent was distilled off under reduced pressure, followed by recrystallization from ethyl ether, whereby 4,4-dimethyl-1,1-(ethylenedioxy)-3-(phenylsulfonyl)-

cyclohexane was obtained in the form of white crystals.
Yield: 84%
4,4-Dimethyl-1,1-(ethylenedioxy)-3-(phenylsulfonyl)-cyclohexane
Molecular weight: 310 ($C_{16}H_{22}O_4S$)
Melting point: 113 to 115°C
TLC: (hexane-AcOET: 6-4) Rf=0.36
^{1}H NMR (200 MHz, $CDCl_3$), δ:1.27 (s,3H,H-7); 1.34-1.41(m,1H,H-5); 1.37(s,3H,H-8); 1.45-1.78(m,4H,H-2e,5,6); 2.01(t,^{3}J=13.1 Hz,1H,H-2a); 3.15(dd,^{3}J=13.1 Hz,^{3}J=3.4 Hz,1H,H-3); 3.6-3.93(m,4H,O-CH_2-CH_2-O); 7.50-7.67(m,3H,H ar.-3',4'); 7.86-7.90(m,2H,H ar.-2').
^{13}C NMR (50 MHz, $CDCl_3$), δ:20(C-7); 30.6(C-8); 30.8(C-6); 32.5(C-2); 34.5(C-4); 40.8(C-5); 64(O-$\underline{C}H_2$-CH_2O); 64.3(O-CH_2-$\underline{C}H_2$O); 68.8(C-3);108.1(C-1);128.3(C ar.-2'*);129(C ar.-3'*);133.3(C ar.-4');139.9(C ar.-1').
Analysis(%): calculated C:61.91, H:7.14; found: C:62, H:7.1

(3) A solution of n-butyl lithium (2.93 ml) was added dropwise to a solution of 930 mg of 4,4-dimethyl-1,1-(ethylenedioxy)-3-(phenylsulfonyl)-cyclohexane and 4 mg of triphenylmethane in 5 ml of THF at -78°C under an argon stream. After stirring for 10 minutes, the mixture was reacted at room temperature for one hour. HMPA (1 ml) was added to the reaction mixture, followed by recooling to -78°C. A solution

of 236 mg of 10-bromo-1-decanol in 2 ml of THF was added dropwise to the reaction mixture.

After the reaction at -20° C for 2 hours, the reaction mixture was poured into a saturated solution of ammonium chloride. The resulting mixture was extracted with ethyl ether. The organic layer was washed with water and saturated saline, and dried over magnesium sulfate. The solvent was then distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column while using hexane-ethyl acetate, whereby 4,4-dimethyl-1,1-(ethylenedioxy)-3-(10-hydroxydecyl)-3-(phenylsulfonyl)-cyclohexane was obtained in the form a colorless oil. Yield: 94%

4,4-Dimethyl-1,1-(ethylenedioxy)-3-(10-hydroxydecyl)-3-(phenylsulfonyl)-cyclohexane

Molecular weight: 466 ($C_{26}H_{45}O_5S$)

TLC: (hexane-AcOET: 6-4) Rf=0.15

^{1}H NMR (200 MHz, $CDCl_3$), δ :1.17 (s,3H,H-17); 1.05-1.4(m,14H,H-8 to H-14); 1.42(s,3H,H-18); 1.49-1.64(m,2H,H-15); 1.77-2(m,4H,H-2,6); 2.6(d,J_{gem}=14.3 Hz,1H,H-2); 3.65(t,J=6.3 Hz,2H,H-16); 3.77-3.96(m,4H,O-CH_2-CH_2-O); 7.47-7.66(m,3H,H ar.-3',4'); 7.83-7.88(m,2H,H ar.-2').

^{13}C NMR (50 MHz, $CDCl_3$), δ :24.1(C-14); 25.4(C-17,18); 25.7(C-7); 29.5(C-10 to C-13); 30.2(C-8); 31.1(C-2*); 31.5(C-6*); 32.7(C-15); 33.3(C-9); 38.1(C-4); 38.6(C-

5);62.9(C-16);63.8,64.7(O-$\underline{C}H_2$-$\underline{C}H_2$-O); 75(C-3); 108.9(C-1); 128.8(C ar.-2'); 129.8(C ar.-3'); 133.2(C ar.-4'); 140.7(C ar.-1').

IR(KBr):3474, 3064, 2925, 2853, 1590, 1464, 1447, 1297, 1135, 1078, 729, 692.

MS(Cl-NH_3): 484.3(MNH_4^+,12); 327.3(44); 326.3(22); 325.3(M-SO_2Ph,100); 282.2(5); 265.2(6); 255.2(5); 174.9(8); 160(6); 99(17).

(4) Paratoluenesulfonic acid (20 mg) was added to a solution of 400 mg of 4,4-dimethyl-1,1-(ethylenedioxy)-3-(10-hydroxydecyl)-3-(phenylsulfonyl)-cyclohexane in 30 ml of chloroform and 6 ml of acetone. The resulting mixture was reacted at 50°C for 24 hours. To the reaction mixture, were added 10 ml of a saturated sodium bicarbonate solution, followed by extraction with dichloromethane. The organic layer was washed with saturated saline and dried over magnesium sulfate. The solvent was then distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column while using hexane-ethyl acetate, whereby 4,4-dimethyl-3-(10-hydroxydecyl)-2-cyclohexen-1-one was obtained in the form of a colorless oil. Yield: 78%

4,4-Dimethyl-3-(10-hydroxydecyl)-2-cyclohexen-1-one

Molecular weight: 280 ($C_{18}H_{32}O_2$)

TLC: (hexane-AcOET: 6-4) Rf=0.25

^{1}H NMR (200 MHz, $CDCl_3$), δ :1.16 (s,6H,H-17,18); 1.30(s large,12H,H-9 to H-14); 1.42-1.63(m,4H,H-8,15); 1.85(t,J=6.6 Hz,2H,H-5); 2.19(t,J=7 Hz,2H,H-7); 2.44(t,J=6.6 Hz,2H,H-6); 3.64(t,J=6.4 Hz,2H,H-16); 5.79(s,1H,H-2).

^{13}C NMR (50 MHz, $CDCl_3$), δ :25.7(C-14); 26.4(C-17,18); 27.4(C-8); 29.4(C-9 a C-13); 31.9(C-7); 32.7(C-15); 34.2(C-6); 35.6(C-4); 37.9(C-5); 62.9(C-16); 124.2(C-2); 172.9(C-3); 199.6(C-1).

IR(NaCl):3425, 2928, 2853, 1660, 1610, 1464, 1412, 1366, 1330, 1276, 1245, 867.

UV(acetonitrile):λmax:232nm(ε 12120).

MS(EI):280(M^+,24);262.1(M-H_2O,4); 250.1(21); 224(8); 196.1(6); 179($C_{12}H_{19}O$,8); 152.1(12); 151($C_{10}H_{15}O$,100); 138(35); 125.1(34); 124.1(31); 123(39); 121(13); 110(23); 109(27); 107(C_7H_7O,11);96(27); 95(36); 82(12); 81(21); 79(16); 69(15); 67(29); 55.1(33).

Analysis (%):calculated C:77.09, H:11.50; found C:76.3,H:11.4.

Example 12

In a similar manner to Example 11, 3-(11-hydroxy-undecyl)-4,4-dimethyl-2-cyclohexen-1-one was obtained.

Molecular weight: 294 ($C_{19}H_{34}O_2$)

TLC: (hexane-AcOET: 6-4) Rf=0.25

MS(EI):294(M^+,14);276.1(M-H_2O,4); 264.1(23); 249.1(5); 238.1(6); 210.1(4); 195.1(5); 179($C_{12}H_{19}O$,8); 152.1(13);

151($C_{10}H_{15}O$,100); 138(30); 125.1(40); 124.1(31); 123(43); 121(14); 110(24); 109(28); 107(C_7H_7O,10); 97(11); 96.1(25); 95(40); 83.1(11); 82(11); 81(20); 79(16); 69(18); 67(32); 55(38).

Analysis (%):

calculated C:77.50, H:11.64

found: C:77.4,H:11.4.

Example 13

In a similar manner to Example 11, 3-(12-hydroxydodecyl)-4,4-dimethyl-2-cyclohexen-1-one was obtained.

Molecular weight: 308 ($C_{20}H_{36}O_2$)

TLC: (hexane-AcOET: 6-4) Rf=0.27

MS(EI):308(M^+,19);290.1(M-H_2O,5); 278.1(25); 263.1(6); 252.1(6); 209.1(6); 179($C_{12}H_{19}O$,8); 152.1(12); 151($C_{10}H_{15}O$,100); 138(26); 125.1(35); 124(28); 123(40); 121(13); 110.1(18); 109(22); 96(21); 95(32); 82(10); 81(17); 79(12); 69(16); 67(25); 55(37).

Analysis (%):

calculated C:77.87, H:11.76

found: C:78, H:11.7.

Example 14

In a similar manner to Example 11, 3-(13-hydroxytridecyl)-4,4-dimethyl-2-cyclohexen-1-one was obtained.

Molecular weight: 322 ($C_{21}H_{38}O_2$)

TLC: (hexane-AcOET: 6-4) Rf=0.3

GC°: Retention time: 23.4 min (purity>99%)

MS(EI):322.2(M^+,19);304(M-H_2O,6); 292.2(22); 277.1(6); 266.1(5); 223.1(5); 179($C_{12}H_{19}O$,8); 152.1(13); 151($C_{10}H_{15}O$,100); 138(25); 125.1(34); 124.1(28); 122.9(48); 121(14); 110(18); 109(23); 96.1(21); 95(33); 83.1(10); 81(18); 79(12); 69(18); 67(24); 55(40).

Analysis (%):

calculated C:78.20, H:11.88

found: C:78.4, H:11.6.

Example 15

In a similar manner to Example 11, 3-(14-hydroxy-tetradecyl)-4,4-dimethyl-2-cyclohexen-1-one was obtained.

Molecular weight: 336 ($C_{22}H_{40}O_2$)

TLC: (hexane-AcOET: 6-4) Rf=0.3

MS(EI):336.2(M^+,20);318(M-H_2O,6); 306.2(6); 291.2(5); 280.1(5); 237.1(5); 179.1($C_{12}H_{19}O$,9); 152.1(13); 151($C_{10}H_{15}O$,100); 138(30); 125.1(33); 124(29); 122.9(56); 110(17); 109(25); 96.1(22); 95(33); 83.1(12); 81.1(19); 79(12); 69(20); 67(28); 55(40).

Analysis (%):

calculated C:78.51, H:11.98

found: C:78.3, H:12.1.

Example 16

(1) Benzenesulfinic acid sodium salt (2.9 g) was added to a solution containing 1.5 g of 2-methyl-2-cyclohexen-1-one and 8 ml of water. Then 16 ml of 1N hydrochloric acid was added dropwise to the resulting mixture. The reaction

mixture was stirred at room temperature for 24 hours. The crystals so precipitated were filtered and then, washed with water, isopropanol and cold ethyl ether. After recrystallization from isopropanol, 2-methyl-3-(phenylsulfonyl)-cyclohexan-1-one was obtained in the form of white crystals. Yield: 93%

2-Methyl-3-(phenylsulfonyl)-cyclohexan-1-one

Molecular weight: 252 ($C_{13}H_{16}O_3S$)

TLC: (hexane-AcOET: 6-4) Rf=0.25

^{1}H NMR (200 MHz, $CDCl_3$),

-major isomer(cis): δ :1.41 (d, J=7.19 Hz,3H,H-7); 1.49-1.68 (m,1H,H-5); 1.96-2.33(m,4H,H-4,5,6e); 2.57(ddd,J=14.8 Hz,J=12.5 Hz,J=6.2 Hz,1H,H-6a); 2.85-3.01(m,1H,H-2); 3.31 (dt,^{3}J=11.2 Hz,^{3}J=4.1 Hz,1H,H-3); 7.54-7.73(m,3H,H ar.-3',4'); 7.87-7.92(m,2H,H ar.-2').

^{13}C NMR (50 MHz, $CDCl_3$), two isomers are detected:

-trans: δ :14.7(C-7); 22.7(C-5);24.6(C-4); 32.6(C-6); 45(C-2); 68.2(C-3); 128.7(C ar.-2'*); 129.3(C ar.-3'*); 133.9(C ar.-4');138.2(C ar.-1'); 209.2(C-1).

-cis: δ :12.7(C-7); 20.2(C-5);23.2(C-4); 36.9(C-6); 44(C-2); 65(C-3); 128.3(C ar.-2'*); 129.3(C ar.-3'*); 133.9(C ar.-4'); 138.2(C ar.-1'); 209.2(C-1).

(2) To a solution obtained by dissolving 1.4 g of 2-methyl-3-(phenylsulfonyl)-cyclohexan-1-one in 20 ml of benzene, were added 0.41 ml of 1,2-ethanediol and 0.1 g of anhydrous paratoluenesulfonic acid. The resulting mixture

was heated under reflux for 4 hours. After the reaction, a 2M aqueous sodium bicarbonate solution was added and the resulting mixture was extracted with ethyl acetate three times. The combined organic layers were washed with saturated saline and dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was recrystallized from ethyl ether, whereby 1,1-(ethylenedioxy)-2-methyl-3-(phenylsulfonyl)-cyclohexane was obtained in the form of white crystals.

Yield: 95%

1,1-(Ethylenedioxy)-2-methyl-3-(phenylsulfonyl)-cyclohexane

Molecular weight: 296 ($C_{15}H_{20}O_4S$)

Melting point: 76 to 77°C

TLC: (hexane-AcOET: 6-4) Rf=0.4

^{1}H NMR (200 MHz, $CDCl_3$),

-<u>trans</u>: δ :1.24 (d, J=6.8 Hz,3H,H-7); 1.32-1.53 (m, 2H,H-5); 1.60-1.85(m,4H,H-4,6); 2.12(dqa,^{3}J=11.3 Hz,^{3}J=6.8 Hz,1H,H-2); 3.14 (td,^{3}J=11.3 Hz,^{3}J=3.5 Hz,1H,H-3);3.83-3.99(m,4H,O-CH_2-CH_2-O); 7.49-7.68(m,3H,H ar.-3',4'); 7.83-7.93(m,2H,H ar.-2').

-<u>cis</u>: δ :1.24 (d, J=7.1 Hz,3H,H-7); 1.32-1.53 (m,2H,H-5); 1.60-1.85(m,4H,H-4,6); 2.43(qad,^{3}J=7.1 Hz,^{3}J=3.6 Hz,1H,H-2); 3.34 (dt,^{3}J=12.3 Hz,^{3}J=3.6 Hz,1H,H-3); 3.83-3.99 (m,4H,O-CH_2-CH_2-O); 7.48-7.67(m,3H,H ar.-3',4'); 7.8-7.88(m,2H,H ar.-2').

^{13}C NMR (50 MHz, $CDCl_3$),

-trans: δ :11.7(C-7); 21.5(C-5);27.2(C-4); 34.3(C-6); 40.6(C-2); 65.3(O-$\underline{C}H_2$-$\underline{C}H_2$-O); 67(C-3); 110(C-1); 128.5(C ar.-2'*); 129(C ar.-3'*);133.4(C ar.-4');138.7(C ar.-1').

-cis: δ :10.1(C-7); 19(C-5);21.5(C-4); 29(C-6); 36.4(C-2); 63.8(C-3); 64.3(O-$\underline{C}H_2$-$\underline{C}H_2$-O); 110.2(C-1); 128.4(C ar.-2'*); 129(C ar.-3'*); 133.4(C ar.-4'); 139(C ar.-1').

Analysis (%): calculated C:60.79, H:6.8; found: C61, H:6.7

(3) A solution of n-butyl lithium (1.02 ml) was added dropwise to a solution of 304 mg of 1,1-(ethylenedioxy)-2-methyl-3-(phenylsulfonyl)-cyclohexane and 4 mg of triphenylmethane in 5 ml of THF at -78° C under an argon stream. After stirring for 10 minutes, the reaction was effected at room temperature for 1 hour. HMPA (1ml) was added to the reaction mixture. It was then recooled to -78° C, followed by the dropwise addition of a solution of 90 mg of 10-bromo-1-decanol in 2 ml of THF. After reaction at -20° C for 2 hours, the reaction mixture was poured into a saturated solution of ammonium chloride. The resulting mixture was extracted with ethyl ether. The organic layer was washed with water and saturated saline and dried over magnesium sulfate. The solvent was then distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column while using hexane-ethyl acetate, whereby 1,2-(ethylenedioxy)-3-(10-hydroxydecyl)-2-methyl-3-

(phenylsulfonyl)-cyclohexane was obtained in the form of a colorless oil. Yield: 92%

1,1-(ethylenedioxy)-3-(10-hydroxydecyl)-2-methyl-3-(phenylsulfonyl)-cyclohexane

Molecular weight: 452 ($C_{25}H_{40}O_5S$)

TLC: (hexane-AcOET: 6-4) Rf=0.2

^{1}H NMR (200 MHz, $CDCl_3$), δ :1.14 (d,J=6.8 Hz,3H,H-17); 1.27(s large,14H,H-8 to H-14); 1.42-1.75(m,6H,H-5,15); 1.85(qa,J=6.8 Hz,1H,H-2); 2.15-2.33(m,4H,H-4,6); 3.63(t,J=6.5 Hz,2H,H-16); 3.71-4.06(m,4H,O-CH_2-CH_2-O); 7.48-7.67(m,3H,H ar.-3',4'); 7.84-7.89(m,2H,H ar.-2').

^{13}C NMR (50 MHz, $CDCl_3$), δ :7.7(C-17); 18.7(C-5); 23.7(C-14); 25(C-4); 25.6(C-7); 29.4(C-9 to C-13); 30.3(C-8); 32.6(C-15); 34.9(C-6); 43(C-2); 62.6(C-16); 64,65.5(O-$\underline{C}H_2$-$\underline{C}H_2$-O); 72(C-3); 110.3(C-1); 128.6(C ar.-3'*); 130(C ar.-2'*); 133.3(C ar.-4'); 137.2(C ar.-1').

IR(NaCl):3515, 3063, 2926, 2853, 1585, 1286, 1140, 1098, 1083.

(4) Paratoluenesulfonic acid (20 mg) was added to a solution of 388 mg of 1,1-(ethylenedioxy)-3-(10-hydroxydecyl)-2-methyl-3-(phenylsulfonyl)-cyclohexane in 30 ml of chloroform and 6 ml of acetone. The resulting mixture was reacted at 50°C for 24 hours. To the reaction mixture was added 10 ml of a saturated aqueous solution of sodium bicarbonate, followed by extraction with dichloromethane. The organic layer was washed with

saturated saline and dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column while using hexane-ethyl acetate, whereby 3-(10-hydroxydecyl)-2-methyl-2-cyclohexen-1-one was obtained in the form of a colorless oil. Yield: 45%

3-(10-Hydroxydecyl)-2-methyl-2-cyclohexen-1-one

Molecular weight: 266 ($C_{17}H_{30}O_2$)

TLC: (hexane-AcOET: 6-4) Rf=0.2

^{1}H NMR (200 MHz, $CDCl_3$), δ :1.27 (s large,12H,H-9 a H-14); 1.44-1.63(m,4H,H-8,15); 1.76(s,3H,H-17); 1.91(q.J=6.3 Hz,2H,H-5); 2.18-2.41(m,6H,H-4,6,7); 3.64(t,J=6.5 Hz,2H,H-16).

^{13}C NMR (50 MHz, $CDCl_3$), δ :10.5(C-17); 22.4(C-5); 25.7(C-14); 27.3(C-4); 29.5(C-9 a C-13); 30.8(C-8); 32.7(C-15); 35.2(C-7); 37.6(C-6); 62.8(C-16); 130.6(C-2); 159.4(C-3); 199.6(C-1).

IR(NaCl):3455, 2926, 2853, 1665, 1620, 1450, 1120, 1055.

MS(EI): 266.2(M^+,7); 137(51); 125(9); 124(100), 111(15); 109(11); 96(15); 67(11); 55.1(11).

Analysis (%):

calculated C:76.64, H:11.35

found: C: 76.4, H:11.7

Example 17

In a similar manner to Example 16, 3-(11-hydroxyundecyl)-2-methyl-2-cyclohexen-1-one was obtained.

Molecular weight: 280 ($C_{18}H_{32}O_2$)

TLC: (hexane-AcOET: 6-4) Rf=0.24

MS(EI): 280.2(M^+,6); 137(43); 125(9); 124(100), 111(14); 109(9); 96(13); 67(7); 55.1(11).

Analysis (%):

calculated C:77.9, H:11.5

found: C: 76.8, H:11.3

Example 18

In a similar manner to Example 16, 3-(12-hydroxy-dodecyl)-2-methyl-2-cyclohexen-1-one was obtained.

Molecular weight: 294 ($C_{19}H_{34}O_2$)

TLC: (hexane-AcOET: 6-4) Rf=0.26

MS(EI): 294.2(M^+,6); 137(44); 125(10); 124(100), 111(14); 109(9); 96(13); 67.1(7); 55.1(11).

Analysis (%):

calculated C:77.50, H:11.64

found: C: 77.6, H:11.8

Example 19

In a similar manner to Example 16, 3-(13-hydroxy-tridecyl)-2-methyl-2-cyclohexen-1-one was obtained.

Molecular weight: 308 ($C_{20}H_{36}O_2$)

TLC: (hexane-AcOET: 6-4) Rf=0.28

MS(EI): 308.2(M^+,6); 138(6); 137(40); 125(9), 124(100); 111(15); 109(8); 96(11); 55.1(10).

Analysis (%):

calculated C:77.87, H:11.76

found: C: 78., H:11.5

Example 20

In a similar manner to Example 16, 3-(14-hydroxy-tetradecyl)-2-methyl-2-cyclohexen-1-one was obtained.

Molecular weight: 322 ($C_{21}H_{38}O_2$)

TLC: (hexane-AcOET: 6-4) Rf=0.3

MS(EI): 322.2(M^+,6); 137(45); 125(9); 124(100), 111(15); 109(9); 96(10); 67.1(7); 55.1(10).

Analysis (%):

calculated C:78.20, H:11.88

found: C: 78.5, H:11.9

Example 21

To a solution of 1-phenylsulfonyl-2,6,6-trimetyl-1-cyclohexene (1 g, 3.5 mmol, 2 eq.) and triphenylmethane (4 mg) in dry THF (8 ml) was added n-butyllithium (1.4 M in hexane, 4ml, 3 eq.) at -78°C under argon. After stirring for 10 minutes, the mixture was stirred at room temperature and HMPA (1.5 ml) was added. After 1.5 hours at this temperature, the mixture was recooled at -78°C and 11-bromo-undecanol (439 mg, 1.75 mmol, 1 eq.) was added slowly. The mixture was stirred for 3h at -20°C and poured into a solution of saturated NH_4Cl (40 ml). The solution was extracted with ether and the organic layer was washed with brine, dried with $MgSO_4$ and concentrated *in vavuo*. The residue was purified by chromatography over silica gel, eluting with hexane-AcOEt (8-2 to 6-4), to give 1-(12-

hydroxydodecyl-1-phenylsulfonyl)-2,6,6-trimethyl-1-cyclohexene as a white solid (622 mg, 79%).

TLC: (hexane-AcOEt: 5-5) Rf=0.43

^{1}H NMR (200 MHz, $CDCl_3$), δ:0.87 (s 3H,H-19); 0.97(s,3H,H-20); 1.16(s, br.14H,H-10 to H-16); 1.2-1.57(m,8H,H-4,5,9,17); 1.94(s,3H,H-21); 1.98-2.25(m,4H,H-8,3); 3.61(t,J=6.8 Hz,1H,H-18); 3.71(t,J=6.8 HzmlHmH-7); 7.48-7.65(m,3H,H ar.-3',4'); 7.86-7.92(m,2H,H ar.-2').

^{13}C NMR (50 MHz), δ:19(C-4); 23(C-21); 25.7(C-16); 28.5(C-8); 28.9(C-19,20); 29.4(C-9 to C-15); 31.2(C-17); 32.7(C-3); 35.9(C-6); 39.8(C-5); 63(C-18); 67.9(C-7); 128.4(C ar.-2'); 130.5(C-2); 133.5(C ar.-4'); 137.8(C-1); 141.8(C ar.-1').

m.p. 77-78°C

Example 22

To a solution of 1-(12-hydroxydodecyl-1-phenylsulfonyl)-2,6,6-trimethyl-1-cyclohexene (579 mg, 1.29 mmol, 1 eq.) in dry methanol (25 ml) was added sodium phosphate dibasic Na_2HPO_4 (366 mg, 2 eq.) and mercury-sodium amalgam (6% Na, 4 g) at 0°C under argon. The heterogeneous mixture was stirred at room temperature for 4 hours, then quenched with HCl 1N, extracted with ether (3 times), washed with $NaHCO_3$ saturated, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography over silica gel, eluting with hexane-AcOEt (8-2) to give 1-

(12-hydroxydodecyl)-2,6,6-trimethyl-1-cyclohexene as a colorless oil (350 mg, 88%)

TLC: (hexane-AcOEt: 8-2) Rf=0.52

GC:40-280°C(20°C/min) 10.73 min;

^{1}H NMR (200 MHz), δ:0.96 (s,6H,H-19,20); 1.27(s,br,16H,H-9 to H-16); 1.35-1.54(m, 8H,H-4,5,8,17); 1.57(s,3H,H-21); 1.83-2.03(m,4H,H-3,7); 3.62(t,J=6.5 Hz,2H,H-18).

^{13}C NMR (50 MHz), δ:19.6(C-4); 19.8(C-21); 25.7(C-16); 28.6(C-19,20); 28.9(C-8); 29.6(C-9 to C-15); 30.5(C-17); 32.8(C-3*); 32.81(C-7*); 34.8(C-6); 39.8(C-5); 63(C-18); 126.3(C-2); 137.8(C-1).

IR ν:3330(broad,O-H); 2925, 2852(w,C-H): 1466(s,C-H); 1112(s,C-O)

Example 23

To a solution of 1-(12-hydroxydodecyl)-2,6,6-trimethyl-1-cyclohexene (316mg, 1.026 mmol) were added acetic anhydride (7 ml) and pyridine (7 ml). The mixture was stirred at room temperature for 1 hour, then quenched with HCl 5%, extracted with ether, washed with water, dried with $MgSO_4$ and concentrated *in vacuo* to obtain 1-(12-acetoxydodecyl)-2,6,6-trimethyl-1-cyclohexene as a colorless oil (353 mg, 98%).

TLC: (hexane-AcOEt: 5-5) Rf=0.75

GC:40-280°C(20°C/min) 11.02;

^{1}H NMR (200 MHz), δ:0.96 (s,6H,H-19,20); 1.27(s,br,16H,H-9 to H-16); 1.35-1.54(m, 8H,H-4,5,8,17); 1.57(s,3H,H-21);

1.83-2.03(m,4H,H-3,7); 2.04(s,3H,$C\underline{H}_3$-COO); 4.04(t,J=6.6 Hz,2H,H-18).

^{13}C NMR (50 MHz), δ :19.5(C-4); 19.8(C-21); 20.9($\underline{C}H_3$-COO); 25.9(C-16); 28.6(C-19,20); 28.9(C-8); 29.6(C-9 to C-15); 30.5(C-17); 32.7(C-7*); 32.75(C-3*); 34.8(C-6); 39.9(C-5); 64.6(C-18); 126.3(C-2); 137.8(C-1); 171.2(CH_3-$\underline{C}$OO).

IR ν : 2925, 2852(w,C-H): 1744(w,C=O); 1466(s,C-H); 1238(w,C-O)

Example 24

To a solution of 1-(12-acetoxydodecyl)-2,6,6-trimethyl-1-cyclohexene (321 mg, 0.92 mmol, 1 eq.) in cyclohexane (6 ml) was added water (0.8 ml), ruthenium trichloride hydrate (0.7% mol, 1.3 mg) and 70% t-BuOOH (1.26ml, 10 eq.). The solution was stirred at room temperature for 6 hours, filtered through a pad of celite and poured into a solution of 10% Na_2SO_3. The solution was extracted with ether, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography over silica gel, eluting with hexane-AcOEt (95-15 to 90-10) to give 3-(12-acetoxydodecyl)-2,4,4-trimethyl-2-cyclohexen-1-one as a colorless oil (227 mg, 53%).

TLC: (hexane-AcOEt: 3-7) Rf=0.68

GC:40-280°C(20°C/min) 12.2min, 99%;

^{1}H NMR (200 MHz), δ :1.13 (s,6H,H-19,20); 1.26(s,br,16H,H-9 to H-16); 1.35-1.69(m, 4H,H-8,17); 1.73(s,3H,H-21);

1.78(t,J=7.5 Hz,2H,H-5); 2.02(s,3H,CH_3-COO); 2.11-2.19(m,2H,H-7); 2.43(t,J=6.8 Hz,2H,H-6); 4.03(t,J=6.8 Hz,2H,H-18).

^{13}C NMR (50 MHz), δ:11.5(C-21); 20.9(CH_3-COO); 25.8(C-16); 26.8(C-19,20); 28.8(C-8); 29.1(C-17); 29.5(C-9 to C-15); 30.45(C-7); 34.2(C-5); 36.2(C-4); 37.3(C-6); 64.5(C-18); 130.5(C-2); 165(C-3); 171(CH_3-COO); 199(C-1).

IR ν: 2925, 2852(w,C-H): 1741(w,C=O); 1667(w,C-O); 1607(s,C-C); 1468(s,C-H); 1239(w,C-O).

Example 25

To a solution of 3-(12-acetoxydodecyl)-2,4,4-trimethyl-2-cyclohexene-1-one (132 mg, 0.36 mmol, 1 eq.) in dry methanol (8 ml) was added water (3 drops) and K_2CO_3 (74 mg, 0.54 mmol, 1.5 eq.). After stirring at room temperature for 2.5 hours the solution was neutralized at pH 7 with HCl 5%, extracted with ether, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography over silica gel, eluting with hexane-AcOEt (8-2 to 7-3) to give 3-(12-hydroxydodecy)-2,4,4-trimethyl-2-cyclohexen-1-one as a colorless oil (94 mg, 81%).

TLC: (hexane-AcOEt: 7-3) Rf=0.2

GC:40-280°C(20°C/min) 12min, 99%;

^1H NMR (200 MHz), δ:1.13 (s,6H,H-19,20); 1.26(s,br,16H,H-9 to H-16); 1.35-1.69(m, 4H,H-8,17); 1.73(s,3H,H-21); 1.77(t,J=7.5 Hz,2H,H-5); 2.11-2.19(m,2H,H-7); 2.43(t,J=6.8 Hz,2H,H-6); 3.61(t,J=6.8 Hz,2H,H-18).

^{13}C NMR (50 Mhz), δ :11.4(C-21); 25.7(C-16); 26.8(C-19,20); 28.8(C-8); 29.5(C-9 to C-15); 30.45(C-7); 32.7(C-17); 34.2(C-5); 36.2(C-4); 37.3(C-6); 62.9(C-18); 130.4(C-2); 165.4(C-3); 199(C-1).

IR ν : 3440 (broad OH); 2925, 2852(w,C-H): 1666(w,C=O); 1605(s,C=C); 1467(s,C-H).

Examples 26-29

In a manner similar to each of Examples 21-25, the following compounds are obtained. The parenthetical values indicate Rf values of TLC at hexane: ethylacetate=7.3.

Example 26: 3-(13-hydroxytridecyl)-2,4,4-trimethyl-2-cyclohexen-1-one (Rf=0.2)

Example 27: 3-(14-hydroxytetradecyl)-2,4,4-trimethyl-2-cyclohexen-1-one (Rf=0.25)

Example 28: 3-(15-hydroxypentadecyl)-2,4,4-trimethyl-2-cyclohexen-1-one (Rf=0.29)

Example 29: 3-(16-hydroxypentadecyl)-2,4,4-trimethyl-2-cyclohexen-1-one (Rf=0.26)

Test: Neurite growth stimulating effects

Cultures were performed in accordance with the method as announced by the present inventors [Borg J., et al. Dev. Brain Res. 18, 37(1985)] by using neurons derived from fetal rat cerebral hemisphere. The dissociated cells were seeded at a density of 1.5 X 10^5 cells per dish coated with 35-mm

polylysine. To the dish, a DMEM culture medium supplemented with insulin, transferrin, progesterone, sodium selenite and putescine was added. Each compound was dissolved in ethanol to 5 X 10^{-8} M and cells were cultured without medium change for 3 days. Cultures were then fixed with 2% glutaraldehyde in PBS and neurons were observed and photographed under a phase-contrast microscope. The results are shown in Table 1.

Table 1

Compound	Influence on neurite growth
Negative control	0
Example 8	+++
Example 9	++++
Example 10	++++
Example 12	++
Example 13	+++
Example 14	+++
Example 15	+++
Example 18	++
Example 19	+++
Example 20	++++
Example 27	++++
Example 28	++++
Fibroblast growth factor	++

0: no effect, +: slight effect, ++: moderate effect, +++: strong effect > 160%, ++++: very strong effect > 200%
-: toxic, --: very toxic

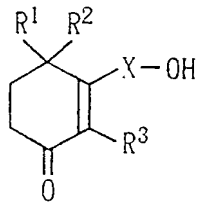
As apparent from Table 1, it has been found that the invention compound (1) has excellent neurite growth stimulating effects even in a markedly low dose.

Industrial Applicability

The invention compound (1) exhibits strong neurite growth stimulating effects so that it is useful as a preventive and/or therapeutic for Alzheimer's disease and the like diseases.

CLAIMS

1. A cyclohexenone long-chain alcohol represented by the following formula (1):



(1)

wherein R^1, R^2 and R^3 each independently represents a hydrogen atom or a methyl group and X represents a C_{10-18} alkylene or alkenylene group.

2. A medicament comprising the compound of Claim 1 as an effective ingredient.

3. A neurite growth stimulating agent comprising the compound of claim 1 as an effective ingredient.

4. A preventive and/or therapeutic for dementia, which comprises the compound of claim 1 as an effective ingredient.

5. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier.

6. Use of the compound of claim 1 as a medicament.

7. A method of treating dementia comprising administering to a patient an effective amount of the compound of claim 1.

INTERNATIONAL SEARCH REPORT

Inter[illegible]nal Application No
P[illegible] 98/03560

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C49/713 C07C403/16 A61K31/12

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C A61K

Documentation searched other than minimumdocumentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 593 831 A (MEDAFOR) 27 April 1994 see claims	1-7
A	WO 91 05754 A (MEDAFOR) 2 May 1991 see page 39 - page 43; claims	1-7

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publicationdate of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of theinternational search	Date of mailing of the international search report
2 November 1998	09/11/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bonnevalle, E

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 98/03560

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 7
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 7 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Interr[redacted]nal Application No
P[redacted] 98/03560

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WO 9105754 A	02-05-1991	FR 2653117 A	19-04-1991
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